IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: Saoud, Christine J.
Avi ASHKENAZI, *et al.*	)	Art Unit: 1647
Application Serial No. 09/904,011	)	Confirmation No: 1120
Filed: July 11, 2001	)	Attorney's Docket No. 39780-1618 P2C8
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING SAME**	)	**Customer No. 35489**

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ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPELLANTS' REPLY BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents -
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On November 24, 2004, the Examiner made a final rejection to pending Claims 39-43. A Notice of Appeal was filed on February 24, 2005, and Appellants' Appeal Brief was filed August 17, 2005.

An Examiner's Answer was mailed on November 10, 2005. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer. This Reply Brief is accompanied by a Request for Oral Hearing.

Priority (35 U.S.C. § 101)

The grounds of rejection in the instant application are a direct result of the determination of priority for the claimed subject matter. Appellants rely for priority on the data derived from the mixed leukocyte reaction (MLR) assay, first disclosed in U. S. Application Serial No. 60/100,858, in order to provide an effective filing date of September 17, 1998.

The Examiner has acknowledged that "the MLR assay is art recognized for identifying molecules which suppress an immune response. It would also be likely that the assay would be useful for identifying molecules which stimulate an immune response." (Page 7 of the Examiner's Answer). Thus it is no longer in dispute that "the results of the MLR assay are generally predictive of *in vivo* effects." (Page 11 of the Examiner's Answer).

Nonetheless, the Examiner's Answer maintains that "the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because one of ordinary skill in the art would not conclude that a molecule which tested positive in the assay of the specification wherein 'positive increases over control are considered positive' would be useful as a molecule for therapeutically enhancing an immune response in an individual (asserted use)." (Page 9 of the Examiner's Answer). The Examiner cites the following arguments in support of this conclusion:

(1) the specification does not provide any values or data for the proteins tested in the MLR assay;

(2) proper art-recognized controls were allegedly not used in the MLR assay described in the specification; and

(3) the specification does not disclose that the results of the MLR assay were statistically significant.

The Examiner's arguments will be addressed in the order they are listed above.

The Examiner asserts that "there is no disclosure, in the specification or in any other source, that the alleged increase reported in the specification for the claimed protein was of any particular degree." (Page 12 of the Examiner's Answer). The Examiner further asserts that "[t]he specification merely demonstrates that the PRO217 protein increases T-cell proliferation above control." (Page 13 of the Examiner's Answer). The Examiner concludes that "further research

would be required to reasonably confirm that the claimed protein stimulates T-cell proliferation to a degree that it would be useful therapeutically for stimulating an immune response, which is the asserted utility in the specification." (Page 16 of the Examiner's Answer).

The specification states that, " Positive increases over control are considered positive with increases of greater than or equal to 180% being preferred. However, any value greater than control indicates a stimulatory effect for the test protein." The specification clearly states that PRO217 (SEQ ID NO: 4) tested positive in this assay, using the described criteria. Example 74 further explains that compounds which stimulate proliferation of lymphocytes in this assay "are useful therapeutically where enhancement of an immune response is beneficial." Accordingly, PRO217 has utility in the treatment of conditions where the stimulation of lymphocyte proliferation would be desirable.

Appellants respectfully submit that the PTO applied an improper legal standard when making this rejection. The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by an Appellant enjoys, or to rebut any statement made by an Appellant in support of utility, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility or any related statement. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant. In addition, according to the Utility Examination Guidelines, Office personnel must treat as true a statement of fact made by an Appellant in relation to an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement.

Appellants respectfully submit that the Examiner failed to meet this evidentiary burden. Appellants in Example 74 indicate that the PRO217 polypeptide tested positive in the MLR assay. Therefore, the Examiner must first provide countervailing evidence to show that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of the data in Example 74. In fact, the Examiner has not provided any evidence that one ordinary skilled in the

art would doubt the credibility of the data in Example 74. Accordingly, the burden to rebut the rejection based on alleged lack of patentable utility has not properly shifted to Appellants.

Example 74 states: "Compounds which stimulate proliferation of lymphocytes are useful therapeutically where enhancement of an immune response is beneficial." The Examiner has acknowledged that the art recognizes the MLR assay as predictive of *in vivo* therapeutic use. Accordingly, a molecule that exhibits a positive response above control in the MLR assay would have therapeutic utility in enhancement of an immune response. The Examiner asserts that "further research would be required to reasonably confirm that the claimed protein stimulates T-cell proliferation to a degree that it would be useful therapeutically for stimulating an immune response." (Page 16 of the Examiner's Answer). As discussed in the M.P.E.P, §2107.03 (V), however, it is improper for Office personnel to request evidence regarding the degree of effectiveness.

Additionally, the Utility Guidelines caution Office personnel to be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the substantial, or "real world" utility prong of the utility requirement. The Examiner has applied an improperly high standard by requiring the Appellants to disclose further experimental details.

The Examiner further asserts that "[t]he assay relied upon on in the instant specification in deficient in that proper art-recognized controls are not present." (Page 14 of the Examiner's Answer).

In particular, the Examiner asserts that

> "[t]he art recognizes several controls as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities...[f]urthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background stimulation or provide for a measure of maximal stimulation." (Pages 8-9 of the Examiner's Answer).

Appellants respectfully submit that the Examiner appears to have misinterpreted the intent of the assay. It is understood that, as the Examiner has stated, the MLR is based upon an

allogenic response. Thus the mixing of the stimulator and responder cells is expected to lead to T cell proliferation even in the absence of any test protein. However, the point of the assay is not to measure the degree to which the stimulator cells induce proliferation of the responder cells. Rather, the point is to measure the extent to which the test protein can enhance the expected proliferation of the stimulated T cells.

Appellants submit that these controls are only needed when the purpose of carrying out the MLR assay is to evaluate the properties of the stimulator cells. As shown, for example, in Figure 16-4 of "Basic and Clinical Immunology, made of record by the Examiner in the Office Action mailed May 10, 2004, the comparisons to mismatched (maximum response) and autologous (background) controls allow one to determine the degree of HLA class II antigen similarity between the stimulator cells and the responder cells. Such determinations, however, are not relevant to the MLR assay of Example 74.

The purpose of the assay disclosed in the instant specification, as discussed above, is to characterize not the stimulator cells, but the test proteins, such as PRO217. The precise extent to which the stimulator cells stimulate the responder cells is not significant; what matters is the degree to which the test protein increases this response. The extent to which the test protein increases the response of the T cells is measured by comparison to a negative control reaction, which uses either cell culture medium, or a non immunostimulant molecule, CD4-IgG, as a negative control. Because the response in the test reaction is compared to a negative control reaction, and because both reactions use the same stimulator and responder cells at the same time, additional controls to determine the precise properties of these cells are not required. The comparison of the test reaction to a negative control using the same cells also serves as an internal control for the inherent day to day variability of cellular responses. Thus the disclosed assay provides all the controls required for the specific purpose of the assay, which is to test whether a PRO polypeptide produces an enhancement of the T cell response over a control using the same stimulator and responder cells.

Finally, the Examiner asserts that "the art accepted standard for determining biological activity is statistical significance. Since no values are provided, statistical significance cannot be ascertained." (Page 20 of the instant Office Action). The Examiner also asserts that "[a]ll assays

have variability and the observed increase over control may be natural variation in the assay, and therefore, not an indication of an immunostimulatory effect." (Pages 17-18 of the Examiner's Answer).

These remarks are a clear indication that the Examiner applies a standard that might be appropriate if the issue at hand were the regulatory approval of a new drug for use in enhancing an immune response, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA, reviewing an application for a new drug will indeed ask for actual numerical data, statistical analysis, and other specific information before a drug is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards of market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States. *Scott v. Finney*, 34 F.3d 1058, 1063, 32 U.S.P.Q.2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson v. Bowler*, 626 F.2d 853, 856, 206 U.S.P.Q. 881, 883 (C.C.P.A. 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement.

That the PTO is applying an inappropriate standard to the evaluation of the MLR assay results is further demonstrated by the contrasting standard applied to the Inhibition of Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth assay (Assay 9), as described in Example 66. The Examiner has stated that the "the claimed invention has met the utility requirement based on its activity of inhibiting VEGF stimulated proliferation of adrenal cortical capillary endothelial cells." (Page 6 of the Examiner's Answer). This assay is also acknowledged to provide enablement for PRO217 (Page 9 of the Examiner's Answer). The protocol and results for the Inhibition of Vascular Endothelial Growth Factor (VEGF) Stimulated Proliferation of Endothelial Cell Growth assay (Assay 9) are described in Example 66.

Appellants note that Example 66 does not provide actual data for PRO217, nor does it provide a statistical analysis of such data. Rather, Example 66 explains the standards used for determination of a positive result ("The results are considered positive if the PRO polypeptide exhibits 30% or greater inhibition of VEGF stimulation of endothelial cell growth (relative

inhibition 30% or greater)"), and states that PRO217 tested positive in the assay. This disclosure is recognized to be sufficient to demonstrate both utility and enablement for PRO217. The disclosure in Example 74, regarding the results of the MLR assay, similarly describes the standards used for determination of a positive result ("any value greater than control indicates a stimulatory effect for the test protein"), and states that PRO217 tested positive in the assay. Thus the amount and type of data provided is essentially the same for both Example 66 and Example 74.

The PTO previously disputed whether results of the MLR assay *in vitro* were reasonably correlated to immunomodulatory activity *in vivo*. The Examiner's Answer acknowledges, however, that "[t]he question of whether the art recognizes the MLR assay as predictive of *in vivo* therapeutic value has been answered." (Page 14 of the Examiner's Answer). Thus there is no reason why a different standard should be applied to the results of the MLR assay, as compared to the proper standard used to evaluate the results of the inhibition of VEGF stimulated cell growth assay.

For the reasons given above, Appellants respectfully submit that the results of the MLR assay as shown in Example 74 of the present specification, and first disclosed in U.S. Provisional Application No. 60/100,858, filed September 17, 1998, provide a specific, substantial and credible utility under 35 U.S.C. §101 for the claimed invention. Accordingly, Appellants respectfully request that the subject matter of the instant claims be granted the September 17, 1998, priority date of U.S. Provisional Application No. 60/100,858.

Claim Rejections Under 35 U.S.C. §102

Claims 39-43 stand rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Hsieh *et al.* (Nature 398:431-436, published April 1, 1999). In addition, Claims 39-43 stand rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Brewer *et al.* (WO 98/54963, published December 10, 1998).

As discussed in the Appeal Brief, Appellants assert that the effective filing date of this application is September 17, 1998, the filing date of U.S. Provisional Application Serial No. 60/100,858, which first disclosed the MLR assay results. Accordingly, neither Hsieh *et al.*

(Nature 398:431-436, published April 1, 1999) nor the PCT patent application by Brewer *et al.* (WO 98/54963, published December 10, 1998) is prior art.

CONCLUSION

For the reasons given above, Appellants submit that the MLR assay disclosed in Example 74 of the specification provides at least one patentable utility for the antibodies of Claims 39-43, and that one of ordinary skill in the art would understand how to used the claimed antibodies, for example in therapeutic applications where enhancement of an immune response is beneficial, such as the treatment of viral infections or cancer. Therefore, Claims 39-43 meet the requirements of 35 USC §101. Further, this patentable utility for the claimed polypeptides was first disclosed in U.S. Provisional Application Serial No. 60/100,858, filed on September 17, 1998, priority to which is claimed in the instant application. Accordingly, the instant application has an effective priority date of September 17, 1998, and therefore Hseih *et al.*, published on April 1, 1999, and Brewer *et al.*, WO 98/54963, published December 10, 1998, are not prior art and do not anticipate the claims under 35 USC §102(a) or (b).

Accordingly, reversal of all the rejections of Claims 39-43 is respectfully requested.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **39780-1618 P2C8**).

Respectfully submitted,

Date: January 10, 2006

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